REMARKS UNDER 37 CFR §1.111

As a preliminary matter, Applicants direct the Examiner's attention to the change in correspondence address and associated change in attorney docket number pursuant to the paper filed herewith.

Applicants acknowledge the current status of the claims as reported in the Office Action mailed 25 June 2002. Claims 1-60, are pending in this application; claims 39-43, and 47-60 are withdrawn from consideration; restriction of the claims has been made final and claims 1-38, and 44-46 are under consideration. Reconsideration and allowance of the application in light of the foregoing amendments and the following remarks are respectfully requested.

Applicants acknowledge the application to be in sequence compliance for Patent application containing nucleotide and /or amino acid sequence disclosures, approval of the formal drawings, and entry of Applicants' IDS.

Applicants note the Examiner's acknowledgement of Applicants' claim for domestic priority under 35 USC §119(e) to provisional application Ser. No. 60/181,608, and also note the Examiner's acknowledgement that Applicants' priority document provides proper support under 35 USC §112 of the IL-18 epitope defined by SEQ ID NO:1 and human monoclonal antibodies to this IL-18 epitope or to intact IL-18. Applicants traverse, however, for reasons discussed *infra*, the Examiner's assertion that the priority document does not appear to support i) IL-18 epitopes of SEQ ID Nos. 3 or 33, ii) antibodies comprising at least one CDR or individual antibody species, or iii) compounds other than antibodies.

Claims 1-3, and 13 are hereby canceled without prejudice to advance examination of the present application to allowance. Applicants reserve the right to prosecute canceled subject matter in a later-filed continuation application, which properly claims the benefit of this application.

Claim 4 is amended to recite the phrase 'A compound comprising ---' in the claim preamble. This amendment is supported throughout the specification as filed, and no new matter is added.

Independent claims 11 and 16 are amended to recite an isolated human antibody or antigen-binding portion thereof, capable of binding IL-18, and, possessing the specific characteristics as recited in the respective claims. This amendment is supported throughout the specification as filed, and no new matter is added.

Claims 11 and 46 are amended to correct obvious typographical errors, so that the claims conform to preferred grammatical structure. Specifically claim 11is amended to conform to proper Markush format. Claim 46 is amended to correct the obvious typographical error of misplaced commas, as noted by the Examiner. In addition, the prefix "anti" is deleted from the claims and the word

"antagonist" is added such that the term "anti TNF" now reads "TNF antagonist". Support for this amendment is specifically found on pages 19-22 of the specification as filed. Applicants assert these amendments: are supported by the application as filed; are obvious on their face; do not add new matter; and are made for reasons unrelated to patentability, but for the purpose of style, grammatical structure, and readability of the claims.

New claim 61 is introduced, directed to preferred embodiments of Applicants' claimed compound comprising a human antibody or antigen-binding portion thereof, capable of binding IL-18 comprising amino acid sequences SEQ ID NO: 70 and SEQ ID NO: 71. Support for this claim is found throughout the specification as filed, particularly at page 2, lines 14-17, and in earlier-canceled claims 1-3. No new matter is added.

Attached hereto as **Appendix A** is a marked-up version of the changes made to the claims by amendment under 37 CFR § 1.121(c)(1)(i). Reconsideration and allowance of the pending claims in light of the foregoing amendments and the following remarks are respectfully requested.

In the Office Action, at page 3, paragraph 60, the Examiner suggests a new title for the present application.

Applicants respectfully request consideration of a new title to be held in abeyance, until final disposition and allowance of the claims in the present application.

Claim objections

In the Office Action, at page 3, paragraph 10, the Examiner has objected to claim 2 for the recitation of non-elected embodiments. Applicants have cancelled claim 2 without prejudice, rendering the objection moot. Applicants respectfully request removal of the objection.

In the Office Action, at page 3, paragraph 11, the Examiner has objected to claim 46 because of informalities, including omission of a comma following "methotrexate" and appearance of extraneous text following the period at the end of the claim. Applicants have amended claim 46 to correct the obvious typographical error of missing a comma following the term 'methotrexate' in the claim, and Applicants have deleted the extraneous text appearing after the period at the end of the claim in accordance with the objection. Removal of the objections to claim 46 respectfully requested.

Claim rejections under 35 USC §112 second paragraph

In the Office Action, at page 3, paragraph 13, claims 1-3, 11-15 and 46 are rejected under 35 USC §112 second paragraph as being indefinite for failing to claim the subject matter of Applicant's invention. Specifically the Examiner asserts:

A) Claim 1-3 are ambiguous and unclear as to the metes and bounds of the claims;

B) Claims 11-15 are improper Markush group format; and

C) Claim 46 is ambiguous as to what additional agents are recited in the claim.

Applicants thank the Examiner for a thorough review of the claims under consideration, and for drawing Applicants' attention to the above-identified typographical errors.

Applicants have canceled claims 1-3 rendering rejection of these claims moot. Applicants reserve the right to prosecute canceled subject matter in a later-filed continuation application, which properly claims the benefit of this application.

Applicants have amended claim 11 to conform to proper Markush format.

Applicants have amended claim 46 to correct the typographical error of misplaced commas within the claim. In addition, the prefix "anti" is deleted from the claims and the word "antagonist" is added such that the term "anti TNF" now reads "TNF antagonist". Support for this amendment is specifically found on pages 19-22 of the specification as filed.

In view of the foregoing amendments and remarks, Applicants respectfully request removal of the rejection of claims 1-3, 11-15 and 46 under 35 USC § 112, second paragraph.

Claim rejections under 35 USC §112 first paragraph

In the Office Action, at page 4-5, paragraph 15, claims 1-3, and 22-38 are rejected under 35 USC §112 first paragraph, as containing subject matter not described in such a way as to convey to one skilled in the art that the Applicant was in possession of the claimed invention. Specifically the Examiner asserts:

a) Claims 1-3 are indefinite as to the disclosure of "compounds capable of binding a human IL-18 amino acid sequence" asserting that Applicants have not described sufficient number of representative species for the exhaustive genus claimed; and

b) Claims 22-38 as indefinite as to the disclosure of antibody or antigen binding portion thereof comprising " at least one variable region CDR" asserting that Applicants do not appear to describe any antibodies in which fewer than six CDRs are defined and which have the function of binding IL-18 or a peptide comprising an epitope of IL-18.

Applicants respectfully disagree and traverse the rejection.

a) The Examiner asserts claims 1-3 are indefinite because Applicants have only disclosed compounds capable of binding a human IL-18 amino acid sequence that are antibodies or antigen-binding fragments. Applicants respectfully disagree and direct the Examiner's attention to page 13, lines 13-16; wherein Applicants teach compounds capable of binding a human IL-18

amino acid sequence can also be peptides, non-peptide based molecules and small molecules having ligand binding activity.

Notwithstanding Applicant's traverse, and without in any way acquiescing to the reasons for the present rejection, Applicants have cancelled claims 1-3 thereby rendering the rejection of claims 1-3 under 35 USC §112 first paragraph moot.

b) The Examiner asserts claims 22-38 are indefinite because Applicants do not appear to describe any antibodies in which fewer than six CDRs are defined. Applicants respectfully disagree and direct the Examiner's attention to, for example, page 12, lines 4-28 of the specification as filed, wherein Applicants teach and disclose examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR).

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 1-3 and 22-38 under 35 USC §112 first paragraph.

In the Office Action, at page 5, paragraph 16, the Examiner has rejected claims 1-3, and 22-38 under 35 USC §112 first paragraph, because the specification, while enabling for antibodies and antigen binding fragments thereof in which 3 CDRs in the VH region and 3 CDRs in the VL region are defined, does not provide enablement for antibodies and antigen binding fragments thereof comprising less that three heavy chain and three light chain CDRs.

Applicants disagree for the reasons stated *supra.* In the specification as filed, on page 12, lines 4-28, Applicants teach and disclose examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR).

Applicants assert the fact that not all of the CDRs of the antigen binding site may be necessary (or even utilized) in binding a specific antigen, and that functional antibody fragments comprising fewer than all 6 CDRs is well known by practitioners skilled in the art. Further support for Applicants' position is provided, for example, by the disclosure of Ward *et al.*, (1989) *Nature* 341:544-546 (a photocopy of

which, **marked Exhibit A**, is provided herewith for the convenience of the Examiner), wherein they demonstrate that isolated VH domains, comprising less than the six CDRs which make up an antibody, can and do bind antigen with high affinities.

Applicants, therefore, submit that compounds comprising less than six CDRs capable of binding an antigen with high affinities are known in the art, and Applicants' specification as filed fully enables such human antibodies and antigen binding portions thereof, which are capable of binding human IL-18.

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 1-3 and 22-38 under 35 USC §112 first paragraph.

Claim rejections under 35 USC §102(a)

In the Office Action, at page 8, paragraph 19, claims 1-2, 11-12, and 14-15 are rejected under 35 USC §102(a) as being anticipated by Ho et al. (WO 00/56771). The Examiner asserts that Ho et al., teach neutralizing monoclonal antibodies capable of binding IL-18, and that IL-18 inherently comprises SEQ ID NO: 3 and SEQ ID NO: 33, thereby anticipating Applicants' claimed invention. Applicants respectfully disagree.

35 U.S.C. §102, in relevant part, states that:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, **before the invention thereof by the applicant for a patent**. [emphasis added].

Ho et al., WO 00/56771, was published on 28 September 2000.

Applicant's priority document (Ser. No. 60/181,608), wherein Applicants teach and disclose antibodies capable of binding IL-18, was filed on 2 February 2000.

The filing date of Applicants' priority document antedates the Ho et al. reference by almost eight months. At the time of filing of Applicants' application, Ho et al. was unavailable to the public. The Ho et al. publication, therefore, is unavailable as a reference under 35 U.S.C. §102(a). Accordingly, the rejection of claims 1-2, 11-12, and 14-15 under 35 USC §102(a) as anticipated by Ho et al., WO 00/56771 should be withdrawn.

Notwithstanding Applicant's traverse, and without in any way acquiescing to the reasons for the present rejection, Applicants have cancelled claims 1-2, and have amended independent claim 11 (from which claims 12, 14, and 15 depend) to recite an isolated human antibody or antigen-binding portion thereof, capable of binding IL-18. Ho et al., do not teach or disclose a human antibody or antigen binding portion thereof, capable of binding IL-18.

In view of Applicants' foregoing amendments and remarks, the rejection of claims 1-2, 11-12, and 14-15 under 35 USC §102(a) as anticipated by Ho et al., WO 00/56771 is both improper and obviated. Applicants, therefore, respectfully request withdrawal of the rejection of claims 1-2, 11-12, and 14-15 under 35 USC §102(a).

In the Office Action, at page 8, paragraph 20, claims 16-21 are rejected under 35 USC §102(a) as being anticipated by Yoshihiro et al., (EP 0 974 600). The Examiner asserts that Yoshihiro et al., teach antibodies capable of binding IL-18 and that specific functional properties recited in claims 16-21 "would be" inherent properties of a neutralizing antibody to human IL-18. Applicants respectfully disagree.

It is well established that:

> TO ANTICIPATE A CLAIM THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM
>
> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).
>
> MPEP §2131

The Examiner acknowledges the cited art does not teach or disclose specific properties of the antibodies, including k_{off} rate and IC_{50}. Because the cited reference does not teach or suggest every element of Applicants' invention as claimed (e.g., methods of testing, or identifying antibodies with specific k_{off} rates and IC_{50} values), Yoshihiro et al. fail to anticipate Applicants' invention. That the antibodies disclosed by Yoshihiro et al. would inherently possess the features and characteristics recited in Applicants' claims is mere supposition on the part of the Examiner and improper absent supporting data.

However, again, notwithstanding Applicant's traverse, and without in any way acquiescing to the reasons for the present rejection, Applicants have amended claim 16 to recite an isolated human antibody or antigen-binding portion thereof, capable of binding IL-18. Yoshihiro et al dos not teach or disclose a human antibody or antigen binding portion thereof, capable of binding IL-18.

In view of Applicants' foregoing amendments and remarks, the rejection of claims 16-21 under 35 USC §102(a) as anticipated by Yoshihiro et al., (EP 0 974 600) is obviated. Applicants, therefore, respectfully request withdrawal of the rejection of claims 16-21 under 35 USC §102(a).

Claim rejections under 35 USC §102(b)

In the Office Action, at page 9, paragraph 21, the Examiner has rejected claims 1-2, 11-12, and 14-15 under 35 USC §102(b) as being anticipated by Yoshihiro et al., (EP 0 974 600). The Examiner asserts that Yoshihiro et al., teach monoclonal antibodies capable of binding human IL-18, thereby anticipating Applicants' claimed invention. Applicants respectfully disagree.

35 U.S.C. §102, in relevant part, states that:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, **more than one year prior to the date of application** for patent in the United States. [emphasis added].

Yoshihiro et al. (EP 0 974 600) was published on 26 January 2000.

Applicant's priority document (Ser. No. 60/181,608), wherein Applicants teach and disclose antibodies capable of binding IL-18, was filed on 2 February 2000.

Yoshihiro et al., was published less than one year before the time Applicants filed the provisional Patent application to which their patent application claims priority. Yoshihiro et al., therefore, is unavailable as a reference under 35 U.S.C. §102(b). Accordingly, the rejection of claims 1-2, 11-12, and 14-15 under 35 USC §102(b) as anticipated by Yoshihiro et al., (EP 0 974 600) should be withdrawn.

Again, Notwithstanding Applicant's traverse, and without in any way acquiescing to the reasons for the present rejection, Applicants have cancelled claims 1-2, and have amended independent claim 11 (from which claims 12, 14, and 15 depend) to recite an isolated human antibody or antigen-binding portion thereof, capable of binding IL-18. Yoshihiro et al., do not teach or disclose a human antibody or antigen binding portion thereof, capable of binding IL-18.

In view of Applicants' foregoing remarks, Applicants submit the present invention as claimed is patentably distinguishable from the Yoshihiro et al., (EP 0 974 600) disclosure. Applicants, therefore, respectfully request withdrawal of the rejection of claim claims 1-2, 11-12, and 14-15 under 35 USC §102(b).

Claim rejections under 35 USC §103(a)

In the Office Action, at page 9, paragraph 23, claims 1-24 and 44-46 are rejected under 35 USC §103(a) as being unpatentable over Kucherlapati et al., (US Patent No. 6,075,181) and Dinarello et al., (J. Leukoc. Biol. 1998; 63:658-664). The Examiner asserts Kucherlapati et al., teach a method of producing fully human monoclonal antibodies to any protein of interest. The Examiner acknowledges that Kucherlapati et al. do not teach human antibodies to IL-18. The Examiner asserts Dinarello et al., teach cloned and recombinantly produced human IL-18. The Examiner asserts the ordinary artisan at the time the invention was made would have been motivated to combine the two cited references and produce fully human monoclonal antibodies that could bind and neutralize IL-18. Applicants respectfully disagree traverse the rejection.

35 U.S.C. §103(a), in relevant part, states that:

> (a) a patent may not be obtained though the invention is not identically disclosed or set forth in **section 102** of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. [emphasis added].

35 U.S.C. §102, in relevant part, states that:

> A person shall be entitled to a patent unless –
>
> (a) the invention was **known or used** by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. [emphasis added].

MPEP § 2132, in relevant part, states that:

> "Known or Used" Means Publicly Known or Used
>
> "The statutory language 'known or used by others in this country' (35 U.S.C. §102(a)), means knowledge or use which is accessible to the public." *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

Kucherlapati et al., (US Patent No. 6,075,181) issued and published on 13 June 2000.

Applicant's priority document (Ser. No. 60/181,608), wherein Applicants teach and disclose antibodies capable of binding IL-18, was filed on 2 February 2000.

The filing date of Applicants' priority document antedates the Kucherlapati et al., reference by over four months. At the time of filing of Applicants' application, Kucherlapati et al., was unavailable to the public. The Kucherlapati et al., publication, therefore, is unavailable as a reference under 35 U.S.C. §102(a). Accordingly, the rejection of claims 1-24 and 44-46 under 35 U.S.C. §103(a) over Kucherlapati et al., in view of Dinarello et al. should be withdrawn.

Notwithstanding Applicant's traverse, and without in any way acquiescing to the reasons for the present rejection, Applicants have cancelled claims 1-3, and have amended independent claims 11 (from which claims 12, 14, and 15 depend) and 16 to recite an isolated human antibody or antigen-binding portion thereof, capable of binding IL-18. Dinarello et al., do not teach or disclose a human antibody or antigen binding portion thereof, capable of binding IL-18.

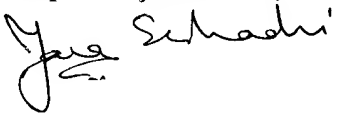
In view of Applicants' foregoing remarks, Applicants submit that the rejection of claims 1-22, and 44-46 under 35 U.S.C. §103(a) as being obvious over Kucherlapati et al., (US Patent No. 6,075,181) in view of Dinarello et al., (J. Leukoc Biol. 1998; 63:658-664), is both improper and obviated.

Applicants, therefore, respectfully request withdrawal of the rejection of claims 1-22, and 44-46 under 35 U.S.C. §103(a).

Conclusion

In view of the foregoing amendments and remarks, Applicants believe the rejections set forth in the Office Action dated 17 June 2002 have been avoided or overcome and consequently their application is in condition for allowance. Applicants, therefore, respectfully request reconsideration and removal of the rejections, and allowance of the pending claims as amended.

Respectfully submitted,



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APPENDIX A

CLAIM AMENDMENTS UNDER 37 CFR §1.121(c)(1)(ii):
VERSION WITH MARKINGS TO SHOW CHANGES MADE

4. (Amended) A compound comprising a human monoclonal antibody, or antigen-binding portion thereof, capable of binding to human IL-18.

11. (Amended) An isolated human antibody, or an antigen-binding portion thereof, that binds an epitope of human IL-18, or portion thereof, comprising an amino acid sequence selected from the group ~~comprising~~ consisting of SEQ ID NO: 3 and SEQ ID NO: 33.

16. (Amended) An isolated human antibody, or antigen-binding portion thereof, that binds to an epitope of human IL-18, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $0.1s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of 1×10^{-6}M or less.

46. (Amended) The pharmaceutical composition of claim 45, wherein said additional agent is selected from the group consisting of an antibody[,] or fragment thereof[,]capable of binding human IL-12, methotrexate, [~~anti-~~]TNF antagonists, corticosteroids, cyclosporin, rapamycin, FK506, and non-steroidal anti-inflammatory agents.~~an~~